

Scalable Aerobic Oxidation of Alcohols Using Catalytic DDQ/HNO₃

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Supporting Information

ABSTRACT: A selective, practical and scalable aerobic oxidation of alcohols is described using catalytic amounts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and HNO₃, with molecular oxygen serving as the terminal oxidant. The method was successfully applied to the oxidation of a wide range of benzylic, propargylic and allylic alcohols, including two natural products, namely carveol and podophyllotoxin. The conditions are also applicable to the selective oxidative deprotection of PMB ethers.

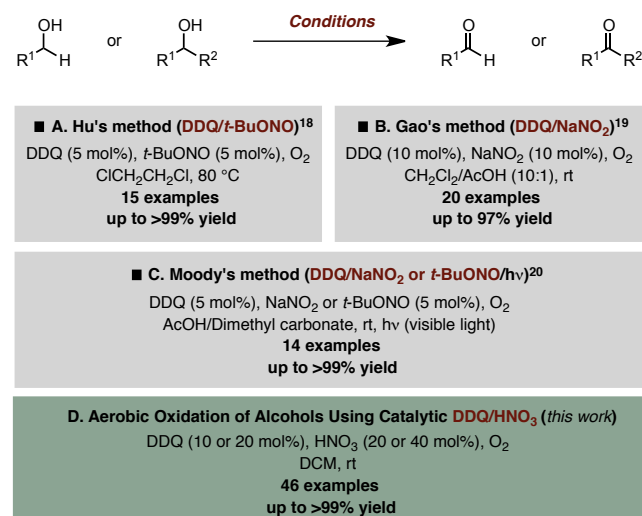
KEYWORDS: Oxidation, alcohols, catalytic, DDQ, HNO₃, aldehydes, ketones.

INTRODUCTION

Oxidation reactions play an important role in organic chemistry as showcased by the number of methods and reagents that have been developed over the years.¹ More specifically, the selective oxidation of alcohols to the corresponding carbonyl compounds is a key transformation with broad applications in the pharmaceutical and agrochemical industry.² Numerous protocols have been developed to perform such oxidations using either high oxidation state metal salts³ or various non-metallic oxidants such as hypervalent iodine,⁴ TEMPO^{2a} and peroxides,^{2b-c} however these methods can present various drawbacks such as their cost or the inherent toxicity of the reagents used or the waste produced.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)⁵ is a well-known oxidant which has been successfully applied to numerous organic transformations, including alcohol oxidation,⁶ protecting group removal,⁷ aromatization,⁸ benzylic acetoxylation,⁹ oxidative coupling,¹⁰ oxidative cyclization¹¹ and biaryl construction¹² just to name a few. Nonetheless, despite its efficiency, the stoichiometric use of DDQ often causes purification difficulties in large-scale syntheses, usually associated with the concomitant formation of the corresponding hydroquinone (DDHQ) in equimolar quantities. In addition, DDQ is relatively expensive and poses some

Figure 1. Oxidation methods using catalytic DDQ.



toxicity concerns due to the release of stoichiometric amounts of HCN upon workup.¹³

To address these limitations, a promising alternative is to combine DDQ with a less expensive, readily available and environmentally benign co-oxidant. In this context, several stoichiometric inorganic co-oxidants have been used in combination with catalytic amounts of DDQ, such as MnO₂,¹⁴ PbO₂,¹⁴ Mn(OAc)₃,¹⁵ Fe(NO₃)₃¹⁶ and FeCl₃.^{7a,17} The use of molecular oxygen as a readily available, non-toxic, inexpensive and more sustainable co-oxidant is an appealing alternative, unfortunately in the absence of any other redox compound, O₂ fails to regenerate DDQ from DDHQ. Over the past years, various groups have been interested in developing an aerobic oxidation involving DDQ. Hu and co-workers for instance showed that *tert*-butyl nitrite (TBN) in conjunction with molecular oxygen could readily convert DDHQ into DDQ, and thus used this system to oxidize non-sterically hindered benzylic alcohols (Figure 1, A).¹⁸ In 2012, Gao and co-workers developed a practical process for the oxidation of alcohols to the corresponding carbonyl compounds using catalytic amounts of DDQ and NaNO₂ and molecular oxygen as

Table 1. Systematic study.^a

c1ccccc1C(O)c2ccccc2 (1a)
 $\xrightarrow[\text{Solvent (0.2 M), O}_2, \text{rt}]{\text{DDQ (10 mol\%), HNO}_3 \text{ (20 mol\%)}}$
c1ccccc1C(=O)c2ccccc2 (2)

Entry	Solvent	Time (h)	Yield ^b (%)
1	THF	18	<5
2	Me-THF	18	<5
3	DME	18	<5
4	MTBE	18	<5
5	DCE	18	64
6	DCM	18	77
7	DCM	4	28
8	DCM	8	46
9 ^c	DCM	18	85

^a All reactions were run on a 1.1 mmol scale at room temperature.^b Isolated yield. ^c Reaction run using 20 mol% of DDQ and 40 mol% of HNO₃.

the terminal oxidant (Figure 1, **B**).¹⁹ Finally, Moody and co-workers developed a photochemical oxidation of benzylic and allylic alcohols using DDQ and sodium nitrite or *tert*-butyl nitrite (TBN) as co-catalysts and molecular oxygen as the terminal oxidant under visible light irradiation (Figure 1, **C**).²⁰

Following the recent developments in the area, we became interested in developing a practical, cost-effective and scalable oxidation process using HNO₃ as a source of NO to regenerate DDQ from DDHQ, and molecular oxygen as the terminal oxidant (Figure 1, **D**). We report here the results of our endeavour.

RESULTS AND DISCUSSION

We initiated this study using diphenyl methanol **1a** as a model substrate running the reactions in a sealed tube using 10 mol% of DDQ and 20 mol% of HNO₃ at room temperature for 18 h. The results are summarized in Table 1.

A rapid evaluation of the set up showed that running the reaction in a sealed tube fitted with an oxygen balloon led to better results than running the reaction in an open flask or under molecular oxygen bubbling. The evaluation of a series of solvents also showed that THF, Me-THF, DME or even MTBE, which is ideal for industrial use, led to poor yields (Table 1, entries 1-4), while chlorinated solvent such as DCE and the DCM afforded the desired ketone **2** in 64 and 77% yield, respectively (Table 1, entries 5 and 6). The high yield and, most importantly, the low flammability of DCM compared to DCE, made this solvent particularly suitable for the development of a potential aerobic oxidation process.

Increasing the catalyst loading from 10 mol% to 20 mol% of DDQ and from 20 mol% to 40 mol% of HNO₃ led to the best results with up to 85% isolated yield (Table 1, entry 9).

With these optimized conditions in hand [DDQ (20 mol%), HNO₃ (40 mol%), DCM, rt, 18 h], we next evaluated the substrate scope. It is worth pointing out however that some substrates were readily oxidized using only 10 mol% of DDQ and 20 mol% of HNO₃. The results are summarized in Scheme 1.

A series of diarylmethanol were first subjected to the DDQ/HNO₃-catalyzed oxidation conditions. The corresponding diaryl ketones **2-16** were obtained in moderate to excellent yields mostly depending on the substitution pattern on the aromatic rings. As a general trend, the more electron-rich precursors led to the highest yields, with the *para*-methoxy derivatives **7** and **14** obtained in quasi-quantitative yield. More sterically hindered substrates such as the ones bearing a substituent at the *ortho* or the *meta* position led to lower yields compared to the corresponding *para*-substituted ones. Two aryl-heteroaryl alcohols were also evaluated. The reactivity of these heterocyclic substrates appeared to decrease when the basicity of the heterocycle increased as showcased by the higher yield obtained in the case of the thiophene derivative (**18**, 79%) compared to the furan (**17**, 40%).

A number of aryl alkyl methanol derivatives were also evaluated resulting in a similar trend, with the more electron-rich substrates such as *para*-methoxyethanol (**22**, 93%), 1-(2*H*-1,3-benzodioxol-5-yl)ethan-1-ol (**23**, 77%), 1-(4-biphenyl)-1-ethanol (**24**, 90%) and α -methyl-2-naphthalenemethanol (**26**, 77%) converted in good to excellent yields. Interestingly, the cyclopropyl derivative **21** was obtained without any noticeable ring opening albeit in a moderate 28% yield.

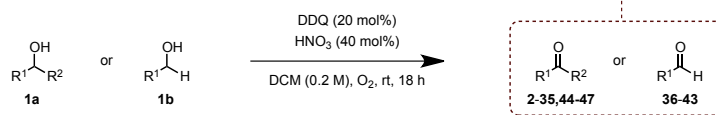
Various bicyclic aryl alkyl derivatives such as flavan-4-ol (**28**, 25%), 1,2,3,4-tetrahydro-1-naphthol (**29**, 58%) and 1-indanol (**30**, 55%) were also tested, however, these substrates appeared to be slightly less reactive as showcased by the lower conversions observed after 18 h.

In an effort to generalize the method, aryl propargyl and aryl allyl alcohols were also tested and the corresponding ketones **31-35** were obtained in high yields ranging from 75% to >99%.

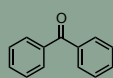
The method was also successfully applied to the synthesis of aromatic (**36-40**) and α,β -unsaturated aldehydes (**41-43**), which were generally obtained in moderate to excellent yields starting from the corresponding benzylic and allylic alcohols.

The chemoselectivity of the reaction was also evaluated by applying our conditions to diol **44**. As expected, only the benzylic alcohol was oxidized albeit in a low 15% yield.

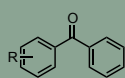
●----- Aerobic Oxidation of Alcohols Using Catalytic DDQ/HNO₃



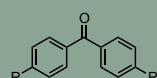
Aryl-Aryl ketones



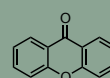
2, 85%
(89% on a 2 gram scale)
(99% on a 150 gram scale)



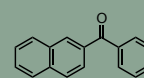
3, *o*-Me, 61%
4, *m*-Me, 68%
5, *p*-Me, 82%
6, *m*-OMe, 22% (49%^b)
7, *p*-OMe, 98%^c



8, R=Br, R'=H, 13% (30%^b)
9, R=Cl, R'=H, 52% (99%^b)
10, R=NO₂, R'=H, 15% (34%^b)
11, R=NMe₂, R'=H, 42%
12, R=Ph, R'=H, 92%
13, R=R'=F, 56% (80%^b)
14, R=R'=OMe, >99%^c

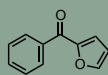


15, >99%^c

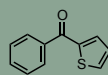


16, 90%

Aryl-Heteroaryl ketones



17, 40%



18, 79%

Aryl-Alkyl ketones



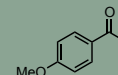
19, 42%



20, 54% (95%^b)

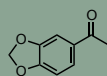


21, 28%

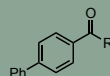


22, 93%

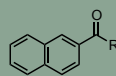
Aryl-Alkyl ketones



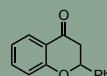
23, 77%



24, R=Me, 90%^c
25, R=*n*-Bu, 32% (78%^b)



26, R=Me, 77%^c
27, R=*n*-Bu, 80%



28, 25%

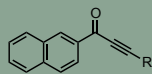


29, 58% (92%^b)



30, 55% (76%^b)

Aryl-Propargyl ketones



31, R=H, 92%^c
32, R=Ph, 94%^c
33, R=TMS, 90%^c



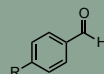
34, 75%

Alkyl-Vinyl ketones

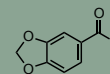


35, >99%

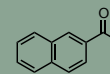
Aromatic / α,β -unsaturated aldehydes



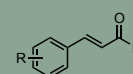
36, R=H, 37%
37, R=Ph, 86%
38, R=OMe, 42%



39, 87%

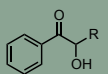


40, 96%^c

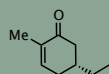


41, R=*o*-Me, 18% (32%^b)
42, X=*p*-Me, 39% (76%^b)
43, X=*p*-Ph, 34%

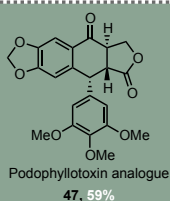
Selectivity & late-stage oxidation



44, R=H, 16%
45, R=Ph, 55%^c



46, 66%
L-Carvone



47, 59%
Podophyllotoxin analogue

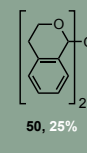
Gram scale oxidation of isochroman



48, 34%
Isochroman **48**
(gram scale)

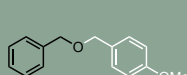


49, 34%

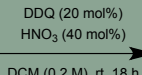


50, 25%

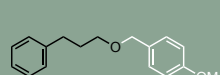
Selective oxidative PMB-deprotection



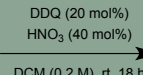
51



36, 68%



52



53, 49% (66%^b)

Scheme 1. ^a All the reactions were run on a 0.5 mmol scale unless otherwise noted using 20 mol% of DDQ, 40 mol% of HNO₃, O₂ (balloon), DCM, rt for 18 h. ^b Yield based on recovered starting material (brsm). ^c The reactions were run using 10 mol% of DDQ and 20 mol% of HNO₃.

With these results in hand and with the idea to showcase further the synthetic utility of the method, we applied our conditions to the oxidation of two

natural products, namely L-carveol and podophyllotoxin. Both were converted to the corresponding ketones **46** and **47** in descent yields ranging from 59% to 66%

(Scheme 1). The scope of the method could even be extended to isochroman derivatives, which also appeared to be good candidates. Indeed, subjecting isochroman **48** to our conditions led to isochromanone **49** in 34% yield, along with 25% of the corresponding dimer **50**, which was quantitatively converted to ethoxy-isochroman-2-one in the presence of ethanol.

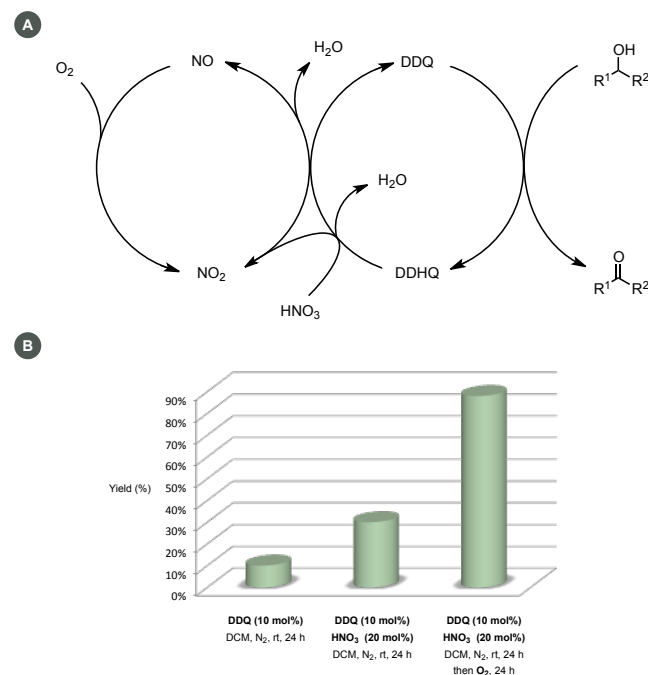
Finally, following the work of Hu and co-workers on the oxidative deprotection of PMB ethers using their DDQ/*t*-BuONO/O₂ system,¹⁸ we were wondering if our own system could reach the same outcome. To validate this hypothesis, we applied our conditions to PMB-protected benzyl alcohol **51**. Interestingly, we were able to isolate benzaldehyde (**36**) in 68% yield, resulting from the deprotection and concomitant oxidation of benzyl alcohol. In contrast, when applying the conditions to ether **52**, we only observed the formation of alcohol **53** in 49% yield, showcasing once again the chemoselectivity of our catalytic DDQ/HNO₃-mediated oxidation method.

After assessing the scope of the method, we eventually evaluated its scalability by performing a first reaction on a two-gram scale. To our delight, diphenyl methanol **1a** was converted to the corresponding ketone **2** with a similar efficiency (89% yield). A much larger scale was also conducted (150 gram batch; 7 L reactor). The corresponding diphenyl ketone was obtained in 99% isolated yield after simple aqueous workup and concentration to dryness (96.9% chemical purity determined by UPLC). It is worth pointing out that a solvent swap from DCM (reaction and extractive solvent) to any other solvent can easily be performed after the workup thus avoiding any isolation step. In order to minimise any potential risk associated with the use of oxygen, we used air instead.

Safety hazards have also been evaluated by DSC (done at the beginning of the reaction). The plot showed a weak exothermic phenomenon ($\Delta H = -34 \text{ J.g}^{-1}$) initiated at 184 °C (*T*_{onset}) and extended until 267 °C, while the related enthalpy of decomposition showed a weak temperature rise of the mixture ($\Delta T_{ad} < 50 \text{ °C}$, adiabatic temperature rise) (see SI for more details). Evaluation of the thermal behavior of the reaction showed no rapid heat generation or rapid decomposition and no risk of explosive hazards could be detected. Overall, the process was ruled safe and amenable to scale-up.

The introduction of air by bubbling did however need to be assessed as it caused the release of hazardous nitrous gas outside the reactor which could potentially pose some health & safety concerns but also some reactivity issues as reactive species are expelled from the reaction vessel during the process. To circumvent the latter issue, a second recharge of DDQ (0.1 equiv.)/HNO₃ (0.2 equiv.) was operated, which allowed to reach quasi complete conversion of the starting material (98% conv.). This gas releasing issue will be further examined for future developments. In

Figure 2. Proposed mechanism for the DDQ/HNO₃-mediated aerobic oxidation.



particular, we will look at implementing in pressure vessels and flow chemistry.

Based on the literature^{18,21} and on the results obtained so far, the following mechanism is proposed featuring two synergistic catalytic cycles where DDQ acts as a catalyst for the oxidation of the substrate, nitric acid as a source of NO₂ that allows the regeneration of DDQ, and molecular oxygen which serves as a terminal oxidant. This mechanism is supported by the control experiments run under a nitrogen atmosphere using either 10 mol% of DDQ or a combination of 10 mol% of DDQ and 20 mol% of HNO₃ (Figure 2, B). It is worth pointing out that a full recovery of the reactivity is observed upon addition of molecular oxygen.

In conclusion, we have developed an efficient catalytic system using DDQ/HNO₃/O₂ for the selective oxidation of benzylic, propargylic and allylic alcohols to the corresponding carbonyl compounds. The method is both practical and scalable and applicable to a wide range of alcohols. Interestingly, the same catalytic method can also be applied to the deprotection of PMB ethers.

EXPERIMENTAL SECTION

Typical procedure for the DDQ/HNO₃-catalysed oxidation. To a solution of the alcohol precursor (1 equiv.) in DCM (0.2 M) at room temperature is added DDQ (0.2 equiv.) followed by a 2M aqueous solution of HNO₃ (0.4 equiv.). The reaction vessel is then sealed and fitted with a balloon of O₂. The reaction mixture is allowed to stir at the same temperature for 18 h, time after which the reaction is quenched with a saturated aqueous solution of NaHCO₃ and extracted with DCM.

The combined organic phases are then dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure to afford a crude residue, which is purified by flash column chromatography over silica gel.

ASSOCIATED CONTENT

Supporting Information

The Supporting information is available free of charge on the Publications website. Details of experimental procedures, ^1H and ^{13}C NMR spectra, DSC study.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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